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MOLECULAR MECHANISMS OF TUMOR CELL RESISTANCE TO THE FGFR KINASE INHIBITOR

DOCTORAL DISSERTATION

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Abstract

Fibroblast Growth Factor Receptor (FGFR) signaling constitutes one of the most prominent pathways involved in cell growth and development as well as cancer progression. All members of the FGFR family have oncogenic gene alterations involved in some human cancers. For instance, FGFR1 amplification is found in the bladder, gastric, breast, and lung cancers, while liver, uterine, lung, and gastric cancers may exhibit FGFR2 amplification, mutations, and fusions. Bladder and lung cancers frequently display FGFR3 mutations and fusions. This indicates that FGFR is a potential target for the new anti-cancer treatment.

This study was aimed at identification of potential biomarkers indicating cancer cells sensitivity/resistance toward a novel small-molecule pan-FGFR inhibitor developed by Polish pharmaceutical company Celon Pharma S.A. Within previous project (CELONKO project; STRATEGMED II program financed by NCBR) RNA sequencing (RNA-seq) experiment was conducted on cell lines that were either resistant or sensitive to that inhibitor. Using the RNA-seq data, a comprehensive analysis of gene expression in cell lines from three different cancer types (lung, stomach, and bladder) was performed to identify potential predictive biomarkers related to mechanisms of FGFR tyrosine kinase inhibitors (FGFR-TKIs) resistance.

To address the limitations of standard analytical methods in low sample size experiments, which often yield results that do not meet the requirements of clinically suitable biomarkers, the "Pipeline for Rapid Evaluation, and Discovery of Important biomarker CandidaTes" (PREDICT) was developed. Applying statistical properties implemented in the PREDICT pipeline, resulted in smaller numbers of candidate biomarkers, however, with more promising properties. Importantly, by removing numerous uncertain candidates, PREDICT pipeline application may reduce the number of entities entering the validation phase what could lead to cost- and effort reduction in biomarker discovery.

Based on signaling pathway analysis, combined with the use of PREDICT pipeline and literature search, it was possible to uncover the link with potential resistance mechanisms towards FGFR-TKIs for the majority of selected genes. These findings indicate that resistant tumor cells exhibit compensatory activation of pathways regulating cell proliferation, migration rate, survival, invasiveness, and antiapoptotic properties, in response to FGFR-TKIs treatment.

By comparing gene sets selected in three different cancer types, several potentially universal biomarkers of FGFR-TKIs resistance were identified, including *SSRP1* (Structure Specific Recognition Protein 1), *CCNB2* (Cyclin B2), *CDT1* (Chromatin Licensing And DNA Replication Factor 1), and *CENPO* (Centromere Protein O). These genes were commonly dysregulated in both stomach and bladder cancer and showed the same direction of change in expression in these two cancer types. They may serve as universal biomarkers for predicting FGFR-TKIs resistance in patients with diagnosed stomach or bladder cancer.

In conclusion, the use of the PREDICT pipeline led to the filtering out the unwanted results, and the selected biomarker candidates possess characteristics suitable for a biomarker that can be applied in clinical settings. An extensive literature search uncovered the link with potential resistance mechanisms towards FGFR-TKIs for the majority of selected genes.